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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,326	02/24/2004	Fredric J. Cohen	X-11057C	9685

25885 7590 12/10/2008

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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
12/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/785,326	COHEN ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19 and 145-156* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19 and 145-156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 19 and 145-156 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/13/2008 has been entered.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 10/13/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Response to Arguments

Applicant's arguments filed 10/13/2008 have been fully considered but they are not persuasive. Applicants present the following arguments.

Firstly, Applicants argue that claim 145 is directed to a "method for reducing the likelihood of incurring or developing estrogen-dependent breast cancer in a post-menopausal woman diagnosed as being in need of such therapy." (emphasis in original). Applicants assert that there is no discussion in Black about diagnosing or screening patients, who are to be administered raloxifene for osteoporosis, for breast cancer risk reduction or prevention. As such, Applicants submit that there is no teaching and no expectation that women who are so diagnosed represent all post-menopausal women. However, the Examiner respectfully submits that all post-menopausal women are "in need of" reducing the likelihood of incurring or developing estrogen-dependent breast cancer. With regard to diagnosing, Black clearly "diagnosed" the patients being

administered raloxifene by taking patient histories. Also see claim 31 of Black, wherein the human "has been diagnosed as suffering from osteoporosis".

Secondly, Applicants argue that the modifier "about" as it relates to the amount of raloxifene administered in the present claims (i.e., about 60 mg) does not expand the range of raloxifene to include any effective amount. In support of this argument, Applicants refer to page 15, lines 24-32 of the instant specification wherein "about 60 mg" is defined:

> Further, the dosage ranges delineated are based on the hydrochloride salt of the compound of formula I. Therefore, the 60 mg dose is equivalent to 55.71 mg of the free base. One of ordinary skill in the art will be able to calculate the free base equivalent of any salt of a compound of formula I which is pharmaceutically acceptable. **For example**, 'about' 60 mg **would encompass** 55 to 65 mg of raloxifene hydrochloride, while encompassing 51.73 to 60.35 mg of the free base (emphasis added).

However, the Examiner is not persuaded that Applicants have provided a limiting definition of what range of doses is intended to be encompassed by "about 60 mg" as recited in the instant claims. In this regard, it is noted that Applicants are providing an example and are simply indicating that "about" 60 mg would encompass 55 to 65 mg of raloxifene hydrochloride. However, Applicants do not state what doses "about" 60 mg would not encompass. For example, in a broad dose range of 0.1 to 1000 mg/day as suggested by Applicants in the specification (page 15, lines 7-8), 200 mg is reasonably "about 60 mg" as recited in the instant claims. As such, the doses of raloxifene administered in Black to post-menopausal women with osteoporosis reasonably fall within Applicant's claimed "about 60 mg".

Thirdly, with regard to the rejection of claim 19 under 35 U.S.C. 103 as being obvious over Black, Applicants incorporate by reference the above arguments for the 35 U.S.C. 102(b) rejection of claims 145-156. Accordingly, the Examiner refers to the discussion supra with regard to these arguments.

The rejections of claims 19 and 145-156 as being anticipated by and/or obvious over Black et al. are maintained for the reasons of record and as reiterated below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 145-156 are again rejected under 35 U.S.C. § 102(b) as being anticipated by **Black *et al***. (U.S. Patent No. 5,393,763; Issued Feb. 28, 1995).

The instant claims recite a method of reducing the likelihood of incurring or developing estrogen-dependent breast cancer in a post-menopausal woman comprising administering raloxifene. Dependent claims recite the limitation wherein the woman is also diagnosed as having established osteoporosis.

Black *et al*. provides methods for inhibiting the loss of bone and are thus effective for the treatment of osteoporosis (Abstract). One of the most common types of osteoporosis is found in post-menopausal women (col. 1, lines 34-35). The methods of the invention comprise administering an effective amount of a compound of formula I as recited in column 2, lines 25-59. Such compounds include raloxifene as instantly claimed (cols. 7-8 and Examples). Doses of 0.1 to 1000 mg and more typically from about 200 to 600 mg are administered (col. 6, line 68 to col. 7, line 5). The instantly claimed dose is "about 60 mg". The "about" modifier expands the range of raloxifene that can be administered to a patient to reasonably include any effective amount, including those doses recited in Black *et al*. In the examples provided in the reference, raloxifene is administered to "post-menopausal women" (col. 19, lines 15-16 and claim 3), thus teaching the instantly claimed patient population. Claim 2 of the '763 patent recites patients suffering from osteoporosis as instantly claimed in claims 153-156.

As taught in Black, the administration of raloxifene to post-menopausal women is effective to treat osteoporosis, which is caused by the cessation of estrogen production by the ovaries. While estrogen replacement therapy is a recognized treatment for post-menopausal osteoporosis, given at very low levels, long-term estrogen therapy has been implicated in increasing the risk of uterine and breast cancer (Black at col. 1, lines 44-

49). As such, post-menopausal women with osteoporosis, especially those undergoing estrogen replacement therapy, are clearly "at increased risk of incurring or developing breast cancer" as recited in the instant claims.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

In the instant case, it flows from the teachings of Black *et al.* that patients being treated with raloxifene so as to inhibit bone loss will naturally have a reduced likelihood of developing breast cancer. It is clear that Black *et al.* contemplate treating post-menopausal women with raloxifene and further contemplate treating patients having osteoporosis with raloxifene (*i.e.*, the same patient populations as instantly claimed). Because the same patient populations are being treated with the same drug, the instantly claimed result of such treatment would naturally occur in the patients being treated in the '763 patent.

Accordingly, the claims are deemed properly rejected as being anticipated by Black *et al.* Applicants' discovery of an additional, unappreciated result of treating post-menopausal women having osteoporosis with raloxifene is not patentable over the '763 patent.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claim 19 is again rejected under 35 U.S.C. § 103(a) as being unpatentable over **Black *et al***. (U.S. Patent No. 5,393,763; Issued Feb. 28, 1995) as applied to claims 145-156, *supra*.

Black *et al*. disclose as applied *supra*. The reference does not explicitly disclose the instantly claimed administration for at least six months. However, in the absence of a showing of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to administer raloxifene for as long was necessary to inhibit bone loss as disclosed in Black *et al*. As such, because the same patient population is being administered the same active agent, it flows from the disclosure of Black *et al*. that such extended treatment will lead to a reduced likelihood of incurring or developing estrogen-dependent breast cancer in post-menopausal women.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under

37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 19 and 145-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Black *et al***. (U.S. Patent No. 5,393,763; Issued Feb. 28, 1995) in view of **Jones** (U.S. Patent No. 4,418,068; Issued Nov. 29, 1983) (cited by Applicants in IDS filed 2/24/2004) and Jordan (Journal of Cellular Biochemistry, 1995, Suppl. 22, pages 51-57) (cited by Applicants in IDS filed 2/24/2004).

Black *et al*. provides methods for inhibiting the loss of bone and are thus effective for the treatment of osteoporosis (Abstract). One of the most common types of osteoporosis is found in post-menopausal women (col. 1, lines 34-35). The methods of the invention comprise administering an effective amount of a compound of formula I as recited in column 2, lines 25-59. Such compounds include raloxifene as instantly claimed (cols. 7-8 and Examples). Doses of 0.1 to 1000 mg and more typically from about 200 to 600 mg are administered (col. 6, line 68 to col. 7, line 5). The instantly claimed dose is "about 60 mg". The "about" modifier expands the range of raloxifene that can be administered to a patient to reasonably include any effective amount, including those doses recited in Black *et al*. In the examples provided in the reference, raloxifene is administered to "post-menopausal women" (col. 19, lines 15-16 and claim 3), thus teaching the instantly claimed patient population. Claim 2 of the '763 patent recites patients suffering from osteoporosis as instantly claimed in claims 153-156.

As taught in Black, the administration of raloxifene to post-menopausal women is effective to treat osteoporosis, which is caused by the cessation of estrogen production by the ovaries. While estrogen replacement therapy is a recognized treatment for post-menopausal osteoporosis, given at very low levels, long-term estrogen therapy has been implicated in increasing the risk of uterine and breast cancer (Black at col. 1, lines 44-49). As such, post-menopausal women with osteoporosis, especially those undergoing estrogen replacement therapy, are clearly "at increased risk of incurring or developing breast cancer" as recited in the instant claims.

Jones teaches that 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiopene (i.e., raloxifene), its ethers and esters, and the physiologically acceptable acid addition salts thereof are valuable antiestrogens and antiandrogens (Abstract; col. 2, lines 14-47). In this regard, Jones teaches that the compounds of the invention are used as pharmaceuticals for antiestrogen and antiandrogen therapy, especially in treatment of mammary tumors (col. 2, lines 33-36) and can thus be administered in an effective dose to a subject suffering from such a condition (i.e., breast cancer) or at risk of suffering from such a condition (id. at lines 44-47). Suitable acid addition salts include the instantly claimed hydrochloride salt (col. 3, line 65). Test 6 at col. 33, line 60 to col. 35, line 39, demonstrates that administration of raloxifene in doses ranging from 0.1 mg/kg/day to 20 mg/kg/day was effective in the treatment of DMBA-induced mammary tumors in rats, including mammary tumors that were partially estrogen-dependent. With regard to reducing the incidence of breast cancer, the inventors teach that "a most important embodiment of the invention" is a method of alleviating mammary cancers which comprises administering a compound of the invention at an effective rate to a patient suffering from or at risk of such a cancer (col. 37, lines 61-65).

Jordan reviews the biological rationale of using antiestrogens for the prevention of breast cancer. It this regard, Jordan states that it is known from laboratory and clinical studies that antiestrogens protect bone and prevent rat mammary cancer (Abstract) and that a potential beneficial side effect of raloxifene to prevent osteoporosis in postmenopausal women may be a reduction in breast cancer risk (id.). In this regard, the author teaches that rather than selecting women to treat with an antiestrogen to prevent breast cancer (with the added advantage of reducing their risk for osteoporosis and coronary artery disease), it is now possible to consider using safe agents to treat all postmenopausal women to prevent osteoporosis and coronary artery disease, but with the added advantage of preventing breast cancer (page 55, left column).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer raloxifene to post-menopausal women with or without osteoporosis for the purpose of reducing or preventing

osteoporosis as well as the incidence of breast cancer in such patients. As taught in Black, the administration of raloxifene to such patients is effective to treat osteoporosis, which is caused by the cessation of estrogen production by the ovaries. While estrogen replacement therapy is a recognized treatment for post-menopausal osteoporosis, given at very low levels, long-term estrogen therapy has been implicated in increasing the risk of uterine and breast cancer (Black at col. 1, lines 44-49). As such, one skilled in the art would reasonably expect that administration of an agent that acts as an antiestrogen while not causing an estrogenic response would be an effective treatment for osteoporosis in post-menopausal women as taught in Black, while at the same time acting to reduce the risk of breast cancer in these subjects due to its antiestrogenic activity as suggested by Jones and Jordan.

With regard to claim 19, one skilled in the art at the time the invention was made would have been motivated to administer raloxifene for as long as is necessary to maintain therapeutic blood levels for antiestrogenic therapy. As such, there is nothing unobvious about administering raloxifene to post-menopausal women with osteoporosis for "at least six months" as recited in instant claim 19. For example, Black teaches that the compounds of the invention will be administered from once to three times each day, or more often as needed to effectively inhibit the bone loss process (col. 7, lines 2-5).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614